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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,799	11/12/2003	Ilan Kor	1662/53605	7835

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EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	PAPER NUMBER
1626	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/712,799	KOR ET AL.	
	Examiner	Art Unit	
	REBECCA L. ANDERSON	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 18-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7,8,10 and 18-21* is/are rejected.

7)☒ Claim(s) *4,6 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/10/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10 and 18-21 are currently pending in the instant application. Claims 1-3, 5, 7, 8, 10 and 18-21 are rejected. Claims 4, 6 and 9 are objected.

Response to Amendment and Arguments

Applicants' amendment and arguments filed 29 November 2007 have been considered and entered into the instant application.

In regards to the 35 USC 112 1st paragraph rejection of claims 18-21, Applicants' arguments have been fully considered but they are not persuasive. It is noted that Applicants' state that the rejection is in error for the reasons that were detailed in the Amendment filed May 30, 2007, however, no amendment in the instant application was filed 30 May 2007. The last amendment filed in the instant application was 6 March 2007. Applicant also argues that the evidence cited is inadequate. While the specification teaches that ethyl acetate solvate solid of carvedilol Form VI can be formulated into pharmaceutical compositions, the specification does not provide any evidence or showing that the pharmaceutical composition prepared contains Form VI ethyl acetate solvate of carvedilol. The specification does not teach that Form VI will persist after being formulated into a pharmaceutical composition. The evidence to rebut that Form VI will persist after being formulated is adequate and is that Rouhi discloses that the art is well aware of the prospect of possible conversion of one crystalline form into another and that drug companies sometimes trade off polymorph stability with solubility recognizing that they will have to deal with the possibility of an undesired conversion to a more thermodynamically stable form. Applicant has not provided any

evidence or disclosure of how undesired conversion was dealt with, nor has applicant provided any evidence of what form is found in the pharmaceutical compositions prepared. Additionally, it has been shown that the usual procedures for making pharmaceutical compositions, such as ball milling, grinding, and adding water will convert polymorphs to other forms. While Rouhi teaches that pharmaceutical companies are actively seeking new crystalline forms of compounds in order to formulate these new crystalline forms into pharmaceutical compositions, Rouhi does not teach that all pharmaceutical compositions and all methods of preparing pharmaceutical compositions would be able to maintain a new metastable form. Contrary, it is shown that ball milling, grinding and the addition of water will change the form. While US pharmacopia states that conversion can be quite slow and that several polymorphs of crystalline pharmaceutical compounds can exist under normal handling conditions and Haleblian states that phase conversion may be so slow in certain ointment bases that a more soluble metastable form may be safely used, it is noted that while conversion "can" be quite slow, it is not stated to "be" slow, additionally, the preparation of pharmaceutical compounds can utilize conditions more harsh than normal handling conditions which can change the form and Haleblian is discussing only phase conversion in certain ointment bases. While applicant argues the pharmaceutical compositions do not contain solutions, it is noted that the claims do not limit the composition to a solid but just that it comprises the crystalline solid of carvedilol and at least one pharmaceutically acceptable carrier, which can be water. Adding the crystalline solid of carvedilol to water will prepare a solution composition.

In regards to the 35 USC 112 1st paragraph rejection of claims 1-10 and 17-21, applicant has cancelled claim 17. Additionally, the amendment to the claims to limit the claims to the ethyl acetate solvate of carvedilol has overcome the rejection of claims 4, 6 and 9 as these claims include all the data for the PXRD, DSC and FTIR. In regards to claims 1-3, 5, 7, 8, 10 and 18-21, Applicant argues that there is no requirement that applicants describe why they defined their invention in the manner claimed and that there is no requirement that a claim must recite every feature of an invention to satisfy the written description requirement. Applicants argue that the specification clearly conveys to one of ordinary skill in the art that Applicants possessed the invention as defined by the PXRD peaks recited in the claims. Applicants argue that the office action provides no evidence that one of ordinary skill in the art would doubt that the Applicants possessed or had invented the claimed invention. Applicant states that it is well established in the art that a PXRD pattern is characteristic of a particular crystalline form and is used in the art to distinguish that crystalline form from the other crystalline forms. These arguments are not persuasive, for as stated by Applicants' it is well established in the art that a PXRD pattern is characteristic of a particular crystalline form and is used in the art to distinguish that crystalline form from the other crystalline forms. The instant rejected claims do not include the entire PXRD pattern nor the entire DSC or FTIR pattern for the form VI. It is the comparison of peak positions and intensities that will show whether the structures are the same or different (Byrn page 63). An x-ray diffraction pattern is like a "fingerprint" and applicant has not provided why the certain peaks found in the claims are the only required peaks in the x-ray diffraction pattern that

must match as the state of the art is the entire PXRD pattern is compared to determine if the forms differ. The peaks present in the claims 1-3, 5, 7, 8, 10 and 18-21 do not include all peaks of the x-ray diffraction pattern, nor does the specification provide any direction or guidance as to why certain peaks are the only required peaks in the x-ray data or other data. The claims 1-3, 5, 7, 8, 10 and 18-21 are only drawn to certain peaks which is not the entire "fingerprint". The amount of direction present in the specification is the x-ray of form VI solvate. Page 4 discloses the data for a solvate of Form VI. The claims to only certain peaks do not find written description in the specification as the claims do not include the enter "fingerprint" and the specification fails to provide any description as to why the data claimed is characteristic of Form VI and why the entire "fingerprint" is not required.

Applicants' amendment to claim 10 has overcome the 35 USC 112 2nd paragraph rejection.

Applicants' amendment to claim 10 and cancellation of claim 17 has overcome the 35 USC 102(b) rejection of claims 10 and 17 as being anticipated by CHEN.

In regards to the remaining 35 USC 102 rejections, Applicant argues that for the reasons appearing for the enablement rejection, the rejections are in error. This arguement is not persuasive for the same reasons as discussed above for the enablement rejection. Therefore, the rejection is maintained for the pharmaceutical composition claims, which have not been demonstrated to be in Form VI in the instant specification.

In regards to the 35 USC 103(a) rejections of the claims, Applicants arguments have been considered and the rejections are withdrawn. The rejections are withdrawn as the crystalline forms of the primary references of these rejections and the claimed ethyl acetate solvate of carvedilol differ in physical characteristics such as X-ray diffraction patterns of the crystalline solid. As Applicants' ethyl acetate solvate of carvedilol of the instant claims was an unknown substance, there were no known ways of making the claimed compound. That some other crystalline forms such as those disclosed in the primary references might have existed does not make obvious the particular claimed crystalline compound since there could have been no motivation to produce the claimed form when one was not known to exist.

Claim Objections

Claims 4, 6 and 9 are objected to as being dependent upon a rejected base claim, but would appear allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case, Claims 18-21 claim compositions comprising crystalline solid of carvedilol form VI, such as an oral dosage form of a tablet.

The nature of the invention

A pharmaceutical composition comprising Form VI carvedilol.

The state of the prior art

The state of the prior art is that the preparation of pharmaceutical compositions requires, for example, milling, adding, excipients, surfactants, etc. The process of preparing a pharmaceutical composition will cause a specific crystalline form, if in the

metastable state to resort back to the most thermodynamically stable form, which is the form with the lowest vapor pressure. Polymorphs tend to convert from less stable to more stable forms (Rouhi, page 32). It is also the state of the art that an acceptable carrier for a pharmaceutical formulation, such as a suspension, can be water. Dissolving a specific crystalline form in water would put the compound in its free form and not any specific crystalline form. The use of a wrong polymorph of a drug when using an aqueous vehicle may provide a phase conversion from the metastable to stable polymorph (Haleblian et al. page 912).

The predictability or lack thereof in the art

The predictability or lack thereof in the art is that a metastable compound will resort back into its most thermodynamically stable form which would have a different X-ray diffraction pattern. Also, a solution prepared from a specific crystalline form and water would contain the free form of the compound.

The amount of direction or guidance present and the presence or absence of working examples

While the specification has provided processes for the preparation of the crystalline form VI, the specification does not provide examples of processes for preparing pharmaceutical compositions utilizing the crystalline form VI. The specification fails to provide the steps of ensuring that the pharmaceutical compositions will maintain the specific forms as found in the specification and will not resort back to the free form or the most thermodynamically stable form of the compound.

The breadth of the claims

A pharmaceutical composition comprising Form VI carvedilol.

The quantity of experimentation needed

The quantity of experimentation needed is undue. One of ordinary skill in the art, without direction, would be unable to maintain a specific metastable crystalline form upon preparation into a pharmaceutical composition which may require milling or formation of a solution at some time during the process of preparing the composition.

The level of the skill in the art

While the level of skill in the art is high, one of skill in the art would be unable to maintain a specific metastable crystalline form upon the preparation of a pharmaceutical composition without direction and guidance which is not found in the instant specification. One of skill in the art would expect the pharmaceutical composition to contain the most thermodynamically stable form of the compound or the free form of the compound.

Claims 1-3, 5, 7, 8, 10 and 18-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The nature of the invention is carvedilol Form VI. The state of the prior art is that the most useful method to compare X-ray powder diffraction data is to overlay and align the respective films or plots. The ensuing comparisons of peak positions and intensities will show whether the structures are the same or different (Byrn page 63). An x-ray diffraction pattern is like a "fingerprint" and applicant has not provided why the certain peaks found in the claims are the only required peaks in the x-ray diffraction pattern that must match. The peaks

present in the claims 1-3, 5, 7, 8 10 and 18-21 do not include all peaks of the x-ray diffraction pattern, nor does the specification provide any direction or guidance as to why certain peaks are the only required peaks in the x-ray data or other data. The claims 1-3, 5, 7, 8, 10 and 18-21 are only drawn to certain peaks which is not the entire "fingerprint". The amount of direction present in the specification is the x-ray of form VI solvate. Page 4 discloses the data for a solvate of Form VI. Applicant has not provided why the entire "fingerprint" is not being claimed, nor does applicant provide why only certain peaks are found in the claims and not others. The claims to only certain peaks do not find written description in the specification as the claims do not include the enter "fingerprint" and the specification fails to provide any description as to why the data claimed is characteristic of Form VI and why the entire "fingerprint" is not required. Therefore the claims are rejected as there is no written description as to why the data present is the only data required from the "fingerprints" to distinguish Form VI from other forms.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 18-21 are rejected under 35 USC 102(b) as being anticipated by US Patent No. 4,503,067.

US Patent No. 4,503,067 discloses pharmaceutical compositions on column 4, for example, in tablets. Example 2, column 5 discloses crystalline carvedilol which is obtained from recrystallization with ethyl acetate.

Claims 18 and 19 are rejected under 35 USC 102(b) as being anticipated by EP 0918055.

EP 0918055 discloses pharmaceutical use on page 2 as a drug having antihypertrensive activity. Examples 6 and 7 and 8, pages 111, disclose crystalline carvedilol which is recrystallized from ethyl acetate.

Claims 18-21 are rejected under 35 USC 102(b) as being anticipated by EP 0893440.

EP 0893440 discloses carvedilol of form I and II on page 3. Pharmaceutical compositions are disclosed on pages 2 and 3, such as tablets, along with in claim 6, see page 4.

Claims 18-21 are rejected under 35 USC 102(b) as being anticipated by WO 99/05105.

WO 99/05105 discloses carvedilol of form I and II on pages 5 and 6. Pharmaceutical compositions are disclosed on page 4, such as tablets, along with in claim 6, page 9.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 18-21 are rejected under 35 U.S.C. 102 (a) and (e) as being anticipated by WO 02/00216.

WO 02/00216 discloses crystalline carvedilol of form III, IV and V and the solvate of methyl-ethyl-ketone) on pages 5, 15 and 16. Pharmaceutical compositions containing carvedilol are disclosed on pages 17-18, such as tablets.

Claims 18 and 19 are rejected under 35 USC 102(e) as being anticipated by US Pre-Grant Publication No. 2004152756.

US Pre-Grant Publication No. 2004152756 discloses crystalline carvedilol form III and pharmaceutical compositions on page 1.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday from 6:00am until 2:30pm.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Rebecca Anderson/
Primary Examiner, AU 1626

19 February 2008

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